

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

To:

see form PCT/ISA/220

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Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

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FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2004/005756

International filing date (day/month/year)
27.05.2004

Priority date (day/month/year)
07.08.2003

International Patent Classification (IPC) or both national classification and IPC
C07C67/307, C07C69/75, C07C51/363, C07C61/15, C07C251/44

Applicant
HONEYWELL SPECIALTY CHEMICALS SEELZE GMBH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITYInternational application No.
PCT/EP2004/005756

IAP20 Rec'd PCT/PTO 30 JAN 2006

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search. (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/005756

Box No. II Priority

1. ☒ The following document has not been furnished:

☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-6
	No: Claims	7-10
Inventive step (IS)	Yes: Claims	4-6
	No: Claims	1-3
Industrial applicability (IA)	Yes: Claims	1-10
	No: Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)

International application No.

PCT/EP2004/005756

Item V

IAP20 Rec'd PCT TO 30 JAN 2006

The following document is referred to in this communication:

- D1 M. Tordeux *et al.*, J. Fl. Chem., 70, 207-214 (1995) cited in the application
- D2 S. Rozen *et al.*, J. Org. Chem., 56, 4695-4700 (1991)
- D3 C. G. Overberger *et al.*, J. Polym. Science, Part A-1, 10, 2265-2289 (1972)
- D4 EP 0 905 109
- D5 WO 01 90 106
- D6 W. Schneider *et al.*, Ber. 96(9), 2377-2386 (1963)
- D7 K. Kahr *et al.*, Chem. Ber., 93, 132-136 (1960)
- D8 US 6 262 075
- D9 JP 2003 012 304
- D10 US 4 792 618

The present application relates to difluorocyclohexane-carboxylic ester of general formula (I') (claims 7-8), use thereof as intermediates in the manufacture of pharmaceutical products (claim 10) and preparation process thereof extended to any geminal difluoroalkanes (claims 1-6) as well as oximes of general formula (II') (claim 9).

V.1 Novelty - Art. 33(2) PCT

The subject-matters of claims 7 to 10 are not novel in view of the following disclosures:

- D10: compound 3, table 1 and claim 6;
- D9: compound 2, page 2 of the japanese patent with n = 1-10 provided in WPI-abstract;
- D8: preparations 9(a) and 12, col. 33 and col. 35 respectively; in particular col. 33, lines 47-51 and col.35, lines 41-48;
- D7; D6;
- D5: examples 4-5, page 36;
- D4: examples 11-12, page 25;
- D3: compound XI, page 2268 and synthesis thereof on pages 2279-2280.

D2 pertains to the conversion of oxime to CF₂ using IF (table I and description on pages 4698-4699). D1 describes the preparation of geminal dihaloalkanes in particular the difluoro-one compound 5a. Compound 5a is recovered therein from an unsubstituted

oxime (compound 1a) using anhydrous HF in ether in the presence of nitric oxide in 50% yield (pages 212-213: "using other oxidants"). The methyl-substituted difluorocyclohexane, compound 5d, is also indicated in this document (scheme 3).

None of the above-cited documents disclose the process of preparation of difluoroalkanes starting from an oxime in the presence of a nitrite and a complex based on hydrogen fluoride and an organic base. Novelty could be recognized for the process according to claims 1 to 6.

V.2 Inventive step - Art. 33(3) PCT

The closest related process is known from D1. It differs from the presently claimed one in the identity of the oxidant used: nitric oxide instead of a nitrite and the absence of an organic based/HF complex. The technical problem posed in the present application is to provide a process of preparation of geminal substituted difluoroalkanes applicable on an industrial scale, i.e. sufficient high yield and cost-effective reagents. The proposed solution is the process according to claim 1.

2.1 The present application has shown that such a process is solution of the present technical problem working under anhydrous conditions with HF/pyridine as fluorination agent, NaNO_2 as oxidative agent on a carboxylic ester substituted oxime of formula (I') as substrate (examples 1-2). Since not all the essential technical features are present in claim 1, i.e. the anhydrous conditions and the particular substrate a cyclohexyl ring activated on the position 4 by a carboxylic group, no inventive step can be recognized for claims 1-3.

2.2 "Substituted" alkyl, aryl or aralkyl are the possibilities for the structural parameters R' and R'' . It comprises therefore the substitution by everything. In view of the experimental data provided it seems that ring constrain and activation on the para position are necessary for the initial substrate. Therefore the substitution of R and R' is specific. Accordingly only an inventive step could be recognized for the starting material of formula (I') (claims 4-6):

Geminal-Difluorocyclohexane, compound 5a in D1, is recovered from the corresponding unsubstituted oxime (compound 1a) using anhydrous HF in ether in the presence of nitric oxide in 50% yield (pages 212-213: "using other oxidants"). In

this document is the methyl-substituted difluorocyclohexane, compound 5d, also prepared starting from the 1-chloro-1-nitroso-equivalent, i.e. compound 2d (scheme 3; page 212). Preparation of geminal difluorides is possible only in the presence of a strong acid (D1, section 3., page 208, last two paragraphs- page 210, 1st paragraph). Therefore in view of the present disclosure the man skilled in the art would be inclined to pursue such a process on substituted oximes to recover the corresponding substituted geminal difluorides in presence of a strong acid. In the present application such a process according to D1 was performed modifying the oxidant to a nitrite (cf. comparative example 2). The recovered yield was of 7.6%, extremely low. The presence of a complex based on HF and pyridine allows to recover the gem-difluoro products in ca 60% yield (cf. examples 1 and 2). An inventive step could be therefore be recognized for the process according to claims 4-6

V.3 Further comments:

- 3.1 The organic base under claim 1 is preferably an amine. The choice of an ether as outlined on page 3 in the description is questionable. Clarification is accordingly kindly requested to the applicant. If the choice of an ether would remain then the relevance of D1 would be reconsidered for the question of inventive step in view of Et₂O used therein !?
- 3.2 The methods A and B have not been defined when referring to the two illustrative examples (pages 5-6).
- 3.3 Essential technical features are missing in claim 1 contravening to the requirements of article 6 PCT (for argumentation cf. inventive step).